## REMARKS

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action dated July 7, 2004 (the "Office Action"). Applicants have canceled Claim 7 without prejudice. Applicants have amended Claim 17 and have added new Claim 22. Applicants respectfully submit that no new matter is added by these claim amendments or new Claim 22, as will be discussed further below. Accordingly, Applicants respectfully request entry of these amendments. Upon entry of this Amendment, Claims 1-6 and 8-21 are pending in the present application. Applicants address below the concerns raised in the Office Action.

## I. Information Disclosure Statement

Applicants appreciate the Examiner's indication that the Information Disclosure Statement (IDS) received by the United States Patent and Trademark Office on May 8, 2003, while not reviewed by the Examiner as of the date of the outstanding Office Action, will be reviewed and duly noted as such in the next response to Applicants. Applicants also submit herewith a Supplemental IDS to present additional references for the Examiner to review in connection with the above-referenced application.

## II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

### A. Claims 1-11

Claims 1-11 stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. More specifically, the Office Action states that "the specification, while being enabling for a method of treating lymphoma in a subject comprising administering to said subject a radiolabeled chimeric $^{131}$I-81C6, does not reasonably provide enablement for any antibody that binds tenascin, as well as a naked 81C6 antibody." Office Action, page 2. Applicants respectfully disagree with this assertion.

The "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (M.P.E.P. §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Applicants respectfully submit that the specification provides substantial guidance as to how the invention may be carried out with respect to antibodies that bind tenascin as described therein and recited in the pending claims. However, in an effort to expedite

prosecution of some of the pending claims, Applicants have amended Claim 1 to recite that the antibody that binds to tenascin is "coupled to a radioisotope."

Accordingly, Applicants respectfully submit that Claims 1-11 are enabled, and respectfully request withdrawal of the rejection of Claims 1-11 under 35 U.S.C. §112, first paragraph.

**B. Claims 4 and 12-21**

Claims 4 and 12-21 stand rejected under 35 U.S.C. §112, first paragraph, as failing to provide adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials. Applicants respectfully disagree with this assertion.

First, Applicants note that the present invention is directed to the new use of a ***known*** compound. In particular, $^{131}$I-labeled chimeric 81C6 monoclonal antibody was described in U.S. Patent No. 5,624,659 to Bigner et al. Clearly, the new use of a known compound does not present the same issues related to the use of a novel compound with respect to enablement.

Further, as noted above, the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without ***undue*** experimentation." *Id.* (emphasis added). Moreover, Applicants note that it is only required that the specification teach one skilled in the art how to make and use the claimed invention. The issue is not whether "some" experimentation is necessary to optimize the invention; the relevant question is whether the amount of experimentation is "undue."

The Office Action states that "a suitable deposit of the molecules designated as 81C6 for patent purposes, evidence of public availability of the claimed cell lines or evidence of the reproducibility without undue experimentation of the claimed cell lines, is required." Office Action, page 4. Applicants respectfully submit that the claimed cell lines can be reproduced without "undue" experimentation.

In particular, the specification at page 4, line 8 through page 6, line 14, clearly and explicitly provides guidance that enable one skilled in the art to arrive at the chimeric 81C6 monoclonal antibody. Such procedures were previously disclosed in U.S. Patent No.

5,624,659 to Bigner et al., which is incorporated by reference in its entirety in the present application. More specifically, Applicants direct the Examiner's attention to Col. 2, line 39 through Col. 3, line 58 and Col. 7, lines 20 through Col. 14, line 5 of U.S. Patent No. 5,624,659 to Bigner et al.

Applicants further note that Rizzieri et al. Phase 1 trial study of $^{131}$I-labeled chimeric 81C6 monoclonal antibody for the treatment of patients with non-Hodgkin lymphoma. *Blood* 104(3): 642-648 (2004), which was noted by the Examiner in the Office Action as being made of record and note relied upon, provides further support of the sufficiency of the written description. Following the protocol set forth in the present application, the authors of Rizzieri et al. were able to conduct a phase I study of pharmacokinetics, dosimetry, toxicity and response of $^{131}$I anti-tenascin chimeric 81C6 for the treatment of lymphoma.

Thus, as evidenced by the reproducibility of the ***known*** cells lines as referenced in at least issued U.S. Patent No. 5,624,659 to Bigner et al. as well as in Rizzieri et al. (2004), the claimed cell lines can be reproduced without "undue" experimentation.

Accordingly, Applicants respectfully submit that Claims 4 and 12-21 comply with the written description requirement and the enablement requirement of 35 U.S.C. §112, first paragraph, and respectfully request withdrawal of these rejections.

## III. Claim Rejections Under 35 U.S.C. §103

Claims 1-21 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,624,659 to Bigner et al. (the "'659 patent") in view of Rizzieri et al. *Blood* **94(10)** Part 2, Supplement 1: 4339, Abstract #4339 (1999) ("Rizzieri et al. (1999)"). Applicants respectfully traverse this rejection.

Applicants note that in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference or combination of references must teach or suggest all the claim recitations. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837

F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

The '659 patent is directed to treating solid and cystic tumors, in particular brain tumors, that express tenascin. *See* Abstract, Summary of the Invention and Claim 1. As noted in the Office Action, the '659 patent "does not teach a method of treating Hodgkin's lymphoma or Non-Hodgkin's lymphoma, wherein the Non-Hodgkin's lymphoma is unresponsive to rituximab treatment and chemotherapy treatment with 81C6 monoclonal antibody coupled to a radioisotope." Office Action, page 6. As further noted in the Office Action, Rizzieri et al. (1999) discloses that tenascin is found on lymphomatous tissue and delivery of an anti-tenascin antibody may prove to be an effective form of treatment. *See* Office Action, page 6.

Applicants respectfully submit that one of ordinary skill in the art would not be motivated to combine these references where each focuses upon different tumor types. Moreover, one of ordinary skill in the art would not have a reasonable expectation of success given the unpredictability of successfully treating lymphomas. Accordingly, Applicants respectfully submit that the Office Action fails to establish a *prima facie* case of obviousness.

In addition, Applicants further note that "[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness . . . of the claims at issue." M.P.E.P. §716.02(a) citing *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). Moreover, "[a]pplicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage." M.P.E.P. §716.02(a) citing *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).

Applicants respectfully submit that the present invention presents unexpected results with respect to methods of treating lymphoma in a subject in need thereof as recited in Claim 1 and methods of treating Non-Hodgkin's lymphoma in a subject in need thereof as recited in Claim 12. More specifically, the present inventors have shown that an antibody coupled to a radioisotope wherein the antibody binds tenascin is effective in treating lymphoma. In particular, the radiolabeled antibody was thought to be taken up by lymphoma tissue in a manner similar to that seen with normal tissue. In contrast, there was at least a 2-fold greater retention of the radiolabeled antibody in lymphomas as compared to normal tissue. These

unexpected results are submitted concurrently herewith in the Declaration of David A. Rizzieri, M.D. Pursuant to 37 C.F.R. §1.132 (the "Rizzieri Declaration").

As set forth in the Rizzieri Declaration, the present inventors have conducted a phase I study of $^{131}$I-labeled chimeric 81C6 monoclonal antibody for the treatment of patients with non-Hodgkin lymphoma. In particular, the present inventors have studied the pharmacokinetics, dosimetry, toxicity and response of $^{131}$I anti-tenascin human/mouse chimeric 81C6 antibody for the treatment of lymphoma in the absence of any blocking antibodies. Human subjects in this study were selected with relapsed or refractory non-Hodgkin lymphoma who had failed at least one prior regimen without other curative options. Study results revealed rapid uptake in liver and marrow and a slower, but enhanced, uptake in selected tumor sites over normal organs. The estimated average absorbed dose to selected tumors of $^{131}$I anti-tenascin chimeric 81C6 was higher than that obtained from $^{131}$I-tositumomab. These unexpected results obtained from human data support methods of treating lymphoma using an antibody that binds to tenascin in a treatment effective amount as disclosed in the present application.

Accordingly, in view of these unexpected results presenting a significant and practical advantage, Applicants respectfully submit that Claims 1-21 are not obvious under 35 U.S.C. § 103(a) in view of the '659 patent in combination with Rizzieri et al. (1999), and respectfully request withdrawal of these rejections.

## IV. New Claim 22 is Patentable Over the Cited References

New Claim 22 recites as follows:

> 22. A method of treating Non-Hodgkin's lymphoma in a human subject in need thereof, comprising:
> parenterally administering to a human subject afflicted with Non-Hodgkin's lymphoma 81C6 monoclonal antibody coupled to $^{131}$I in an amount of from 10 mCi to 100 mCi, wherein the Non-Hodgkin's lymphoma is unresponsive to chemotherapy treatment.

Applicants respectfully submit that the cited references do not teach or suggest the recitations in new Claim 22. Accordingly, Applicants respectfully submit that new Claim 22 is patentable, and respectfully request entry and allowance thereof.

## V. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

In the event that additional fees are necessary to allow consideration of this paper, such an extension is also hereby petitioned for under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully submitted,

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Susan E. Freedman
Date of Signature: October 5, 2004